UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte GERALD M. **RUBIN**, DUOJIA PAN,
JENNY ROOKE, REZA YAVARI
and TIAN XU

Appeal No. 2004-1106[1]
Application No. 09/871,388[2]

ON BRIEF

Before: WILLIAM F. SMITH, Administrative Patent Judge,
McKELVEY, Senior Administrative Patent Judge, and
SPIEGEL, Administrative Patent Judge.

SPIEGEL, Administrative Patent Judge.

DECISION ON APPEAL

I. Introduction

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final

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[1] The application on appeal was received by the Board on 17 March 2004.

[2] Application for patent filed 31 May 2001. According to appellants, this application is a divisional of application 09/709,126, filed 8 November 200, now U.S. Patent 6,319,704, which is a divisional of application 09/285,502, filed 2 April 1999, now U.S. Patent 6,190,876, which is a divisional of application 08/937,931 filed 27 August 1997, now U.S. Patent 5,935,792, which claims the benefit of provisional applications 60/053,476, filed 23 July 1997, and 60/019,390, filed 29 August 1996. Further according to appellants, the real parties-in-interest are The Regents of the University of California and Exelixis, Inc., the assignee and licensee, respectively, of this application. **However, both the first page of the involved specification and the USPTO assignment records indicate that Yale University is also an assignee.**

rejection of claims 14-21 and 23-33. Claim 22, the only other claim pending in this application, has been indicated as allowable.[3] We **affirm**.

Claims 14-21 and 23-33 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking original descriptive support.

In reaching our decision in this appeal, we have given careful consideration to the appellants' specification and claims and to the respective positions articulated by the appellants and the examiner. We make reference to the EXAMINER'S ANSWER ("Answer," mailed 6 August 2003) for the examiner's reasoning in support of the rejection and to appellant's BRIEF ON APPEAL ("Brief," filed 12 May 2003) and REPLY BRIEF ON APPEAL ("Reply," filed 22 September 2003) for appellants' arguments thereagainst.

Appellants state "all the claims stand as a group" (Brief, p. 2). We, therefore, limit our discussion to claim 14. 37 CFR § 1.192(c)(7).

II. Findings of fact

The following facts are supported by a preponderance of the evidence.

A. KUZ and MADM proteins

1. According to appellants' specification, KUZ refers to a family of proteins encoded by a "new" gene family *kuzbanian (kuz)* which belong to the recently defined ADAM family of transmembrane proteins, members of which contain both A Disintegrin And Metalloprotease domains (p. 2, ll. 6-13).[4]

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[3] See e.g., Final Office Action (issued 11 March 2003, Paper 10), p. 2.

[4] Italics are used herein to refer to a gene, whereas capitals are used to refer to a protein. Thus,

2. SEQ ID NOS: 2, 4, 6 and 8 are said to depict the full length KUZ proteins encoded by SEQ ID NOS: 1, 3, 5 and 7, which are said to depict "exemplary natural cDNAs encoding *Drosophila*, human transmembrane, human soluble (lacking a transmembrane domain), [and] mouse .... members, respectively, of the disclosed KUZ family" (id., p. 4, ll. 9-12).

3. Figures 1A-C of appellants' specification are said to illustrate common predicted functional domains for the described Drosophila KUZ ("DKUZ"), mouse KUZ ("MKUZ") and Xenopus KUZ ("XKUZ"), i.e., a prodomain, metalloprotease and disintegrin domains, a cysteine-rich domain and finally a transmembrane domain (also specification, p. 3, ll. 10-27).

4. These domains, as identified in Figures 1A-C, are said to provide KUZ domain specific activity or function, including protease activity, in particular cleaving a NOTCH protein, disintegrin activity and ligand/antibody binding activity (id., p. 2, ll. 26-30; p. 5, ll. 14-17).

5. The mouse protein (MKUZ) is said to be 45% identical in primary amino acid sequence with Drosophila KUZ (DKUZ, Fig. 1) and 95% identical with a bovine protein (MADM) isolated by Howard.[5] Sequence similarity between MKUZ and DKUZ is said to extend over the whole coding region, except that MKUZ, like other vertebrate KUZ homologs, has a much shorter intracellular domain. The intracellular domain of MKUZ

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kuz is a gene, whereas DKUZ is the protein expressed by the *kuz* gene in Drosophila.

[5] Appellants' specification cites to "the bovine protein of Howard, L., et al. (1996). Biochem. J. *317*, 45-50." at p. 5, ll. 29-31. A copy of this article, i.e., Howard et al., ("Howard"), "Molecular cloning of MADM: a catalytically active mammalian disintegrin-metalloprotease expressed in various cell types," Biochemical Journal, Vol. 317, part 1, pp. 45-50 (1 July 1996), is enclosed.

is said to contain a stretch of 9 amino acid residues that are absolutely conserved with DKUZ. [Id., p. 22, ll. 15-23.]

6. The bovine MADM (i.e., Mammalian Disintegrin-Metalloprotease) protein described by Howard comprises a prodomain (i.e., prosequence), metalloprotease and disintegrin domains, a cysteine-rich domain and finally a transmembrane domain (Howard, p. 48; Figure 5).

7. Howard also describes isolation of rat and human homologs of MADM (abstract; Figure 2, p. 48) as well as raising a polyclonal antiserum in rabbits against a peptide (FDANQPEGKKC) corresponding to amino acids 485-495 of the deduced rat and human polypeptide sequences (p. 47, c. 2, first full ¶; Figure 2, p. 48).

8. The protease domain of MADM contains an extended zinc binding site, HEVGHNFGSPH (residues 383-393), identical to that depicted in appellants' Figure 1A for MKUZ (HEVGNHFGSPH) and substantially identical to that depicted for DKUZ (HEIGHNFGSPH).[6] [Compare appellants' Figure 1A and Howard, p. 48, c. 2, ¶ 2.]

9. According to Howard, MADM had been shown to cleave myelin basic protein (Howard, p. 45, c. 2, ¶ 1) (see also, appellants' specification, p. 22, ll. 16-17).

10. According to appellants' specification, mutant forms of DKUZ containing either a point mutation predicted to abolish protease activity or lacking the protease domain entirely, act in a dominant negative manner in fruit flies, while a truncated form of the

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[6] According to appellants' specification (p. 4, l. 27 - p. 5, l. 1), "[O]ne or more amino acid residues within the sequence can be substituted by another amino acid of a similar polarity which acts as a functional equivalent, resulting in a silent alteration. Conservative substitutes for an amino acid within the sequence may be selected from other members of the class to which the amino acid belongs. For example, the nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine [I], valine [V], proline, phenylalanine, tryptophan and methionine."

mouse homolog of *kuz* which lacked the metalloprotease domain, acted as a dominant negative in fruit flies and in Xenopus embryo, suggesting that the function of *kuz* is evolutionarily conserved (see e.g., Example 3, pp. 20-28).

B. Abbreviated procedural history of the involved application

11. In a preliminary amendment (Paper 1½, filed 31 May 2001), appellants cancelled all pending claims and presented new claims 14-33 for examination. According to appellants, the new claims were "directed to the antibody counterparts of the claims issued and allowed in 09/285,502 and 09/709,126, respectively" (id., p. 6).

12. Claim 14, as presented in the preliminary amendment, read "A composition comprising an antibody or antibody fragment which specifically binds a KUZ polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, and SEQ ID NO:8" (id., p. 4).

13. The examiner rejected claims 14, 17, 20, 21, 23, 25, 26 and 33, as presented in the preliminary amendment, under 35 U.S.C. § 102(b) as anticipated by Howard, the same Howard reference cited by appellants in their specification (Paper 7, mailed 2 October 2002).

14. According to the examiner,

> Howard et al., teaches monoclonal and polyclonal antibody compositions against MADM. Specifically using a peptide sequence FDANQPEGKKC that shares 100% homology with residues 486-496 of SEQ ID NO.8 and shares 9 of 10 amino acid residues with SEQ ID NOS 4 and 6 to make the antibody (page 47, 2nd column in particular). This antibody would inherently specifically bind with SEQ ID NOS 4, 6 and 8 due to the high amino acid sequence homology between the immunizing peptide and the claimed sequences. Furthermore the immunizing peptide is located within the extracellular domain of SEQ ID NO. 4. [Id., p. 2.]

15. In response to this rejection, appellants amended claim 14 to expressly exclude any antibody that specifically binds a MADM protein (Paper 9, filed 24 December 2002).

C. The appeal

16. Claim 14, as amended, is illustrative of the subject matter on appeal and reads

> A composition comprising an antibody or antibody fragment which specifically binds a KUZ polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, and SEQ ID NO:8, **and distinguishes and does not specifically bind bovine mammalian disintegrin-metalloproteinase (MADM)**. [Emphasis added.]

17. The examiner then finally rejected claims 14-21 and 22-33 as lacking original descriptive support for an antibody that binds to SEQ ID NOS: 2, 4, 6 or 8, but does not bind to Howard's MADM protein (Paper 10, mailed 11 March 2003, p. 2).

18. Appellants appealed from the final rejection mailed 11 March 2003 ("NOTICE OF APPEAL," Paper 11, filed 7 May 2003).

19. According to appellants (Brief, pp. 2-3),

> Our Specification teaches that KUZ binding specificity may be assayed by KUZ-specific antibody binding (Specification, p.5, lines 20-24), or by eliciting a KUZ-specific antibody (Specification, p.5, lines 28-29). Our Specification teaches that KUZ binding specificity distinguishes that of bovine MADM (Specification, p.5, lines 29-31). Our specification describes and teaches how to make KUZ-specific antibodies (Specification, p.8, line 18 - p.10, line 8).
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> The objected to limitation is inherent in a KUZ-specific antibody. By specifically binding to the recited KUZ protein, the claimed antibody distinguishes and does not specifically bind bovine MADM. KUZ, by definition, must have a binding specificity that distinguishes MADM. Since KUZ binding specificity by definition includes binding of a KUZ-specific antibody, a KUZ-specific antibody must necessarily distinguish KUZ from MADM.

Other findings of fact follow below.

III. Opinion

A. The legal standard

"The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language." In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983). The written description requirement can be satisfied by showing that the disclosed subject matter, when given its "necessary and only reasonable construction," inherently (i.e., necessarily) satisfies the limitation in question. Kennecott v. Kyocera, 835 F.2d 1419, 1423, 5 USPQ2d 1194, 1198 (Fed. Cir. 1987).

B. Appellants' position

Appellants contend that support for an antibody or fragment thereof which specifically binds one of the recited KUZ proteins but does not specifically bind bovine MADM can be found at page 5, lines 20-24, 28-29 and 29-31 and at page 8, line 18 through page 10, line 8 (FF 14).

20. Specification pages 8 through 10 describe adapting known techniques of producing antibodies or antibody fragments to a generic antigen to production of antibodies or antibody fragments to a specific antigen, i.e., a KUZ protein, derivative or analog (p. 8, ll. 18-19 and 31-32).

21. As noted by the examiner, there is no disclosure of antibodies which specifically bind to the protein defined by any of SEQ ID NOS 2, 4, 6 and 8 but not to MADM

(Answer, p. 4).[7]

22. The last paragraph on specification page 5 (i.e., ll. 14-31) reads:

> The subject domains provide KUZ domain specific activity or function, such as KUZ-specific protease or protease inhibitory activity, disintegrin or disintegrin inhibitory activity, ligand/antibody binding or binding inhibitory [sic], immunogenicity, etc.; see, e.g. domains identified in Fig. 1A-C. Preferred domains cleave a NOTCH protein. KUZ-specific activity or function may be determined by convenient *in vitro*, cell-based, or *in vivo* assays: e.g. *in vitro* binding assays, cell culture assays, in animals (e.g. gene therapy, transgenics, etc.), etc. Binding assays encompass any assay where the molecular interaction of an KUZ polypeptide with a binding target is evaluated. The binding target may be a natural intracellular binding target such as an KUZ substrate, a KUZ regulating protein or other regulator that directly modulates KUZ activity or its localization; or non-natural binding target such [sic] a specific immune protein such as an antibody, or an KUZ specific agent such as those identified in screening assays such as described below. **KUZ-binding specificity may [sic] assayed by protease activity or binding equilibrium constants** (usually at least about 10^7 M^{-1}, preferably at least about 10^8 M^{-1}, more preferably at least about 10^9 M^{-1}), **by the ability of the subject polypeptide to function as negative mutants in KUZ-expressing cells, to elicit KUZ specific antibody in a heterologous host** (e.g [sic] a rodent or rabbit), etc. **The KUZ binding specificity of preferred KUZ polypeptides necessarily distinguishes that of the bovine protein of Howard, L., et al. (1996). Biochem. J. *317*, 45-50.** [Emphasis added.]

23. In essence, appellants' position is that since "KUZ, by definition, must have a binding specificity that distinguishes MADM [... and] KUZ binding specificity by definition includes binding of a KUZ-specific antibody, a KUZ-specific antibody must necessarily [i.e., inherently] distinguish KUZ from MADM" (Brief, p. 3).

C. The examiner's position

24. According to the examiner, "the actual enzymes, the KUZ polypeptides, are

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[7] The pages of the Answer are not numbered. We have considered the cover sheet of the Answer as page 1 and subsequently numbered the remaining pages.

disclosed for distinguishing between the prior art bovine MADM and the disclosed KUZ polypeptides. Nowhere, does Appellant have written support for an antibody that can specifically bind to SEQ ID NOS 2, 4, 6 and 8 and not MADM" (Answer, p. 4). Further according to the examiner, "the term specifically binds in the antibody art does not remove prior art antibodies from reading upon the claimed invention because of art recognized properties of antibody cross reactivity" (id., p. 5).

In other words, we understand the examiner's position to be two-fold. First, the recited KUZ proteins are necessarily distinguishable from bovine MADM based upon their respective enzymatic activity, i.e., KUZ catalyzes cleavage of NOTCH proteins, while MADM catalyzes cleavage of myelin basic protein (FF 4, 9 and 10). Second, a KUZ-specific antibody reads on cross-reactive antibodies, e.g., the MADM antiserum raised against a peptide (FDANQPEGKKC) corresponding to amino acids 485-495 of the deduced rat and human polypeptide sequences described by Howard (FF 7). Therefore, a KUZ-specific antibody does not necessarily, i.e., inherently, fail to bind specifically with MADM.

D. Discussion

Appellants' specification clearly indicates that KUZ binding specificity may be determined, at least, on the basis of (1) protease activity, (2) equilibrium binding constants, (3) ability to function as negative mutants and (4) ability to raise antibody, e.g., antiserum, in a heterologous host, e.g., a rabbit (FF 22). In other words, there is more than one reasonable construction of "KUZ binding specificity." Thus, the binding specificity that distinguishes the recited KUZ proteins from bovine MADM is not

necessarily antibody-based. Rather, as the examiner found, the recited KUZ proteins may be distinguished from bovine MADM based upon their respective enzymatic activities, i.e., MADM cleaves myelin basic protein, whereas KUZ cleaves NOTCH proteins (FF 4, 9 and 10), a substrate-based distinction. Consequently, while KUZ binding specificity may be antibody-based for example, as argued by appellants (Brief, p. 2; Reply, p. 2), antibody binding is not the only reasonable construction of a KUZ specific binding which necessarily distinguishes the preferred KUZ polypeptides of SEQ ID NOS 2, 4, 6 and 8 from the bovine MADM protein of Howard.

Appellants have narrowed their claimed invention to a composition of antibody or antibody fragments which differentiates between homologous proteins found in three specific species, i.e., Drosophila KUZ (SEQ ID NO. 2), human KUZ (SEQ ID NOs 4 and 6) and mouse KUZ (SEQ ID NO. 8), from that found in a fourth specific species, i.e., bovine MADM. However, the primary amino acid sequence of bovine MADM is 95% identical with the primary amino acid sequence of mouse KUZ as defined by SEQ ID NO. 8 (FF 5). Therefore, given the high amino acid sequence identity between MADM and MKUZ, especially in view of the MADM antiserum described by Howard raised against a common peptide sequence, it does not follow that the only reasonable construction of a KUZ specific binding antibody is an antibody that necessarily would not specifically bind to MADM.

Based on the foregoing, the decision of the examiner to reject claims 14-21 and 23-33 for lack of original descriptive support is affirmed.

IV. Miscellaneous

1. Upon return of this application, the examiner may wish to ascertain whether the assignee of the application is correct and, if not, take such action as the examiner deems appropriate.

2. On page 1 of the Reply, counsel asserts that the examination of the application may not have been "impartial." Allegations, assertions and complaints against patent examiners are to appear in "other papers." 37 CFR § 1.3 (2004). Unfortunately, we note that this is not the first time counsel has made such assertions in briefs in cases before this board. See, e.g., pages 1-2 of the REPLY BRIEF ON APPEAL in Appeal No. 2003-1006, involving the same assignee. We believe it appropriate in this appeal to warn counsel that we expect him to refrain in future appeals from including complaints about examiners in appeal brief papers. Rather, a complaint about an examiner may be made in a separate paper addressed to the attention of the Director for Patents. Any further inappropriate activity by counsel in this connection will be referred to the Chief Administrative Patent Judge for such action as the chief deems appropriate.

V. Conclusion

To summarize, the decision of the examiner to reject claims 14-21 and 23-33 under 35 U.S.C. § 112, first paragraph, for lack of original descriptive support is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

WILLIAM F. SMITH
Administrative Patent Judge

FRED E. McKELVEY, Senior
Administrative Patent Judge

) BOARD OF PATENT
) APPEALS
) AND
) INTERFERENCES

CAROL A. SPIEGEL
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